Acupuncture and Amitriptyline for Pain Due to HIV-Related Peripheral Neuropathy

A Randomized Controlled Trial

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Context.—Peripheral neuropathy is common in persons infected with the human immunodeficiency virus (HIV) but few data on symptomatic treatment are available.

Objective.—To evaluate the efficacy of a standardized acupuncture regimen (SAR) and amitriptyline hydrochloride for the relief of pain due to HIV-related peripheral neuropathy in HIV-infected patients.

Design.—Randomized, placebo-controlled, multicenter clinical trial. Each site enrolled patients into 1 of the following 3 options: (1) a modified double-blind 2 × 2 factorial design of SAR, amitriptyline, or the combination compared with placebo, (2) a modified double-blind design of an SAR vs control points, or (3) a double-blind design of amitriptyline vs placebo.

Setting.—Terry Beirn Community Programs for Clinical Research on AIDS (HIV primary care providers) in 10 US cities.

Patients.—Patients with HIV-associated, symptomatic, lower-extremity peripheral neuropathy. Of 250 patients enrolled, 239 were in the acupuncture comparison (125 in the factorial option and 114 in the SAR option vs control points option), and 136 patients were in the amitriptyline comparison (125 in the factorial option and 11 in amitriptyline option vs placebo option).

Interventions.—Standarized acupuncture regimen vs control points, amitriptyline (75 mg/d) vs placebo, or both for 14 weeks.

Main Outcome Measure.—Changes in mean pain scores at 6 and 14 weeks, using a pain scale ranging from 0.0 (no pain) to 1.75 (extremely intense), recorded daily.

Results.—Patients in all 4 groups showed reduction in mean pain scores at 6 and 14 weeks compared with baseline values. For both the acupuncture and amitriptyline comparisons, changes in pain score were not significantly different between the 2 groups. At 6 weeks, the estimated difference in pain reduction for patients in the SAR group compared with those in the control points group (a negative value indicates a greater reduction for the "active" treatment) was 0.01 (95% confidence interval [CI], −0.11 to 0.12; $P = .88$) and for patients in the amitriptyline group vs those in the placebo group was −0.07 (95% CI, −0.22 to 0.08; $P = .38$). At 14 weeks, the difference for those in the SAR group compared with those in the control points group was −0.08 (95% CI, −0.21 to 0.06; $P = .26$) and for amitriptyline compared with placebo was 0.00 (95% CI, −0.18 to 0.19; $P = .99$).

Conclusions.—In this study, neither acupuncture nor amitriptyline was more effective than placebo in relieving pain caused by HIV-related peripheral neuropathy.

JAMA. 1998;280:1590-1595

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PERIPHERAL NEUROPATHIES are diagnosed in 30% to 35% of patients with human immunodeficiency virus (HIV) and cause pain and dysesthesias.[1,2] Symptomatic treatment includes antidepressants, nonnarcotic and narcotic analgesics, anticonvulsants, and acupuncture.[2,3] The use of these treatments is based on anecdotal[4] information and trials in other disease conditions.[5]

We chose to examine the efficacy of 2 commonly used treatments, amitriptyline hydrochloride and acupuncture, for HIV-related peripheral neuropathy. Amitriptyline is frequently prescribed for neuropathic pain and has been shown to be an effective treatment for diabetic, hereditary, toxic, and idiopathic neuropathies.[6,7]

Although several trials that reported examining acupuncture for chronic painful conditions claim efficacy,[8,9] these studies have methodological limitations, including small sample sizes and inadequate controls for the nonspecific effects of acupuncture.[9-11] Meta-analyses of studies of acupuncture for chronic pain show a response rate of approximately 70% for acupuncture, 50% for "sham" acupuncture (needling points not considered effective), and 30% for control treatments, such as sham transcutaneous electrical nerve stimulation.[9,10,12,13]

To evaluate the effect of both a nonstandard and standard medical therapy for peripheral neuropathy, we performed a multicenter, modified double-blind, randomized, placebo-controlled study of the separate and combined efficacy of a standardized acupuncture regimen (SAR) and amitriptyline for the relief of pain caused by HIV-related peripheral neuropathy.

METHODS

Study Design

We used a 2×2 factorial design to determine whether SAR, amitriptyline, or the combination was more effective than placebo. The SAR consisted of acupuncture points chosen by the study acupuncturists and several consultants to be effective for peripheral neuropathic pain. This regimen was compared with control points that were not "true" points defined by any standard acupuncture text[14] (Figure 1). We compared the efficacy of amitriptyline with placebo capsules of identical appearance. Enrollment in the factorial design began in May 1993, but patients at some sites were re-

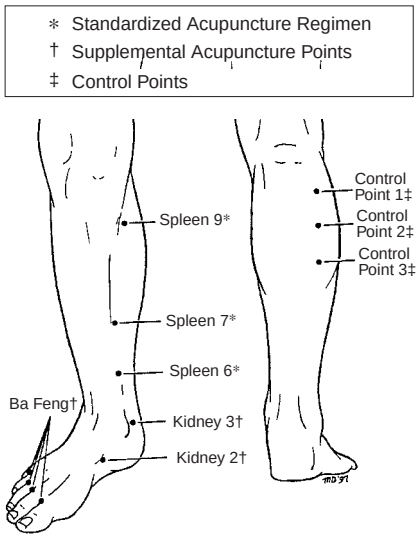

Figure 1.—Standardized acupuncture regimen and control points.

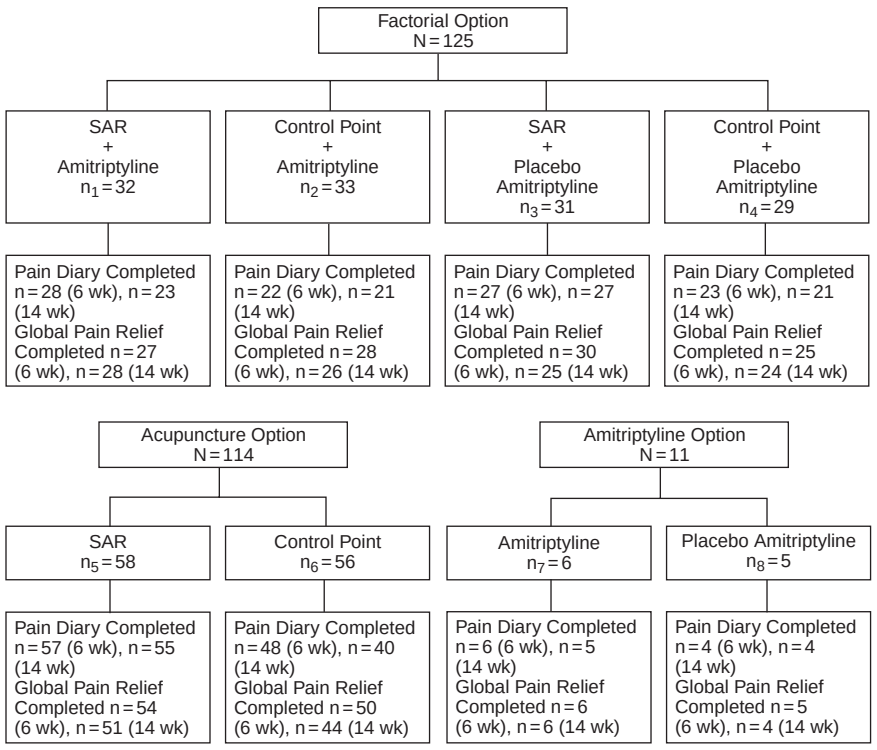

Figure 2.—The standardized acupuncture regimen (SAR) vs control points (CPs) compares $n_1 + n_3 + n_5$ with $n_2 + n_4 + n_6$. The amitriptyline vs placebo compares $n_1 + n_2 + n_7 +$ with $n_3 + n_4 + n_8$.

luctant to be randomized to receive amitriptyline and some clinicians were unwilling to provide amitriptyline to their patients because it was a commonly abused drug in their communities. The study design was modified in March 1995 so that sites could choose only 1 of 3 options. Each site could (1) continue to enroll into the factorial design (factorial option), (2) enroll into a single-factor design of SAR vs control points (acupuncture option), or (3) enroll into a single-factor design of amitriptyline vs placebo (amitriptyline option) (Figure 2).

Randomization schedules were prepared using random blocks stratified by unit. Patients were randomized to treatment by the study units by telephoning the Statistical Center at the University of Minnesota, Minneapolis. The unit pharmacists were the only people unblinded to the placebo vs amitriptyline assignment, and the acupuncturists were the only people unblinded to the SAR vs control points assignments. The pain diaries and the assessments of pain relief were collected by study staff who were blinded to the treatment assignments.

Study Population

Patients were recruited from 11 units of the Terry Beirn Community Programs for Clinical Research on AIDS, an organization sponsored by the National Institutes of Health, which conducts clinical trials in primary care settings. The study was approved by each institutional review board. All participants gave written informed consent. To be eligible, participants had to be aged 13 years or older; have documented HIV infection; have symptoms of HIV-related lower extremity peripheral neuropathy, diagnosed by a physician based on history and clinical examination; and have completed a baseline pain diary prior to randomization. Antiretroviral therapy was allowed and dosages of analgesic medication or herbal therapies used at randomization were maintained or reduced. The initiation of new treatments during the study was discouraged but allowed when necessary. Patients were excluded if they were being treated for an acute opportunistic infection or malignancy except nonsystemic Kaposi sarcoma, were pregnant, or had taken a tricyclic antidepressant or monoamine oxidase inhibitor 2 weeks before randomization.

Treatment Regimens

For the acupuncture comparison, patients were randomly assigned to receive SAR or control points twice weekly during a 6-week induction phase, followed by weekly treatment during an 8-week maintenance phase. This SAR was based on a Chinese theory that peripheral neuropathy caused by diabetes and HIV-related peripheral neuropathy have similar mechanisms. The SAR included spleen points 9, 7, and 6, with the additional supplemental points of Ba Feng (M-LE-8) for complaints of pain or numbness in the toes, Ran Gu (kidney 2) for complaints of pain or numbness in the soles, and Tai Ki (kidney 3) for complaints of pain or numbness in the heel (Figure 1).[14] The control points were located on the back of the leg (Figure 1). For the SAR and control points, acupuncture needles were inserted to a specified depth. Each location was manipulated both superiorly and inferiorly. Then the needles were reinserted into the specified point. After 10 to 15 minutes, the needles were remanipulated and replaced into the original location for another 5 to 10 minutes. The depth of insertion was between 1.28 to 2.54 cm (0.5 to 1.0 in) for spleen point 9, 2.54 to 3.81 cm (1.0 to 1.5 in) for spleen point 7, and 1.5 to 3.05 cm (0.6 to 1.2 in) for spleen point 6. For the control points, insertion was less than 1.28 cm (0.5 in). Study acupuncturists received standardized training in the technique. In addition, a videotape of the acupuncture and the control treatment was provided to each of the acupuncturists in the study. To maintain blinding and to determine the need for supplemental points, the acupuncturists asked all patients a series of standard questions, irrespective of treatment arm. For those in the SAR group, spleen points 9, 7, and 6 were always used. Supplemental acupuncture points were used only if the patient answered "yes" to the corresponding question. The control points consisted of only 3 specified points.

For the amitriptyline comparison, the patients were randomized to receive a 14-week course of either amitriptyline or placebo capsules by mouth once a day.

Table 1.—Baseline Characteristics of Study Participants*

Characteristics	Acupuncture		Amitriptyline Hydrochloride	
	SAR (n = 121)	Control Points (n = 118)	Active (n = 71)	Placebo (n = 65)
Age, mean (SD), y	40.9 (6.8)	41.7 (8.3)	40.1 (7.1)	39.9 (5.9)
Sex, % male	88	92	94	88
Race, %				
Latino/Hispanic	12	6	11	12
Black	30	29	28	22
White	55	61	58	63
Other	3	4	3	3
Baseline pain score, mean (SD)	1.11 (0.3)	1.06 (0.4)	1.10 (0.3)	1.13 (0.3)
Karnofsky score, mean (SD)	84.5 (11.7)	84.7 (11.0)	83.7 (11.5)	83.1 (10.2)
<80, %	21	19	24	15
Disease progression history, %†	53	47	62	48
Current use of antiretrovirals, %	61	65	58	57
Current use of pain medications, %	48	46	47	54
Type of pain, %‡				
Aching/cramping	41	45	51	40
Burning/heat	35	30	28	35
Throbbing	23	22	27	12
Stabbing/sharp	36	36	35	39
Numbness/tingling	88	87	89	86
Other	24	22	30	22

*SAR indicates standardized acupuncture regimen. Values are mean percentage unless otherwise indicated.
†Defined as history of an opportunistic infection or malignancy.
‡These categories are not mutually exclusive.

They were instructed to take them between 1 to 2 hours before bedtime. An initial daily dose of 25 mg of amitriptyline hydrochloride was increased every 2 to 3 days until a maximum dosage of 75 mg/d was reached.[15,16] The placebo capsules were identical in appearance and taste to the active capsules. Patients were followed up for the 14-week study period and for adverse event monitoring for an additonal 8 weeks after the study treatment had discontinued.

Results were monitored by the HIV Therapeutic Trials Data Safety and Monitoring Board of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. Data monitoring used the Lan–De Mets method[17] as a guideline for early stopping to account for increased type I error probability by examining the data before the designed study end.

Evaluation

Patients rated their pain in a diary once daily, choosing from the Gracely scale of 13 words that describe the intensity.[18] The scale ranges from no pain (0.0), weak (0.45), mild (0.74), moderate (1.09), strong (1.36), to extremely intense (1.75). The words had been assigned magnitudes on the basis of ratio-scaling procedures that demonstrated internal consistency, reliability, and objectivity.[18] The scale has distinguished active from control interventions in experimental and clinical pain studies.[6,18,19] At the end of both the induction and maintenance phases, patients reported their global pain relief (complete, a lot, moderate, slight, none, or worse) after they were asked the following question: "Since the beginning of the study, how would you rate the relief of pain and/or discomfort in your legs and feet?" A study physician, trained in neurologic examination, tested the patient at randomization and at 14 weeks. A neurologic summary score was computed as an average of 3 separate scores for muscle strength, sensory ability, and reflex. Each physician who performed the neurologic assessment reviewed a videotape that detailed how the examination was to be completed. The patients also completed a self-administered, 39-item, quality-of-life assessment tool.[20] The complete tool, consisting of 11 different dimensions, was administered at baseline and 14 weeks, and the dimension corresponding to physical functioning was also administered at 6 weeks. To assess the effectiveness of the blinding, all patients were asked to guess their treatment assignments at 14 weeks. Patients were monitored for grade 4 adverse events and death. Adverse experiences occurring within 8 weeks of study treatment were graded on a 5-point severity scale (grade 5 corresponding to death) according to a standardized toxicity scale. Any grade 4 or 5 event was reportable irrespective of presumed relationship to study treatment.

Statistical Analysis

Comparison of treatment groups for the primary end point of change in pain, as measured by the pain diary, used a linear model with baseline characteristics, clinical unit, and option (factorial or single factor) as covariates. If the average weekly pain score for the sixth week of treatment was present, it was used. If it was missing, the closest weekly average within the 6-week visit window of 4 to 10 weeks was used. Similarly, this was done for the 14-week end point and the visit window of 11 to 16 weeks. A linear model repeated measures analysis of the weekly pain averages was also performed, with the same explanatory variables.[21] Estimates of the difference between SAR and control points were calculated for each of the 14 weeks. The global pain relief rating was analyzed using a log-linear model, with likelihood ratio tests for differences among treatment groups, which were adjusted for option.[22]

We verified that results from the 3 treatments could be pooled by checking that the interaction term between acupuncture and amitriptyline in the factorial option and the option by treatment interaction were nonsignificant.

Secondary outcomes were the permanent discontinuation of study treatments, changes in quality of life, and changes in neurologic summary scores, which were analyzed similarly to the primary end point. All analyses were on an intent-to-treat basis. The evaluation of the blinding compared the patients' guesses of the therapy received with the treatment group. Using a log-linear model, we adjusted for option and for whether the patient reported moderate or more pain relief with the 14-week global pain relief rating.

For the original 2×2 factorial design, a sample size of 260 patients was calculated to provide a 90% power of detecting a mean difference between treatments of 0.20 (half the difference between "moderate" and "mild" pain) on the Gracely pain intensity scale using a type I error of .05 (2-sided). After the study design was modified, sample size requirements were estimated at 260 per group. In February 1997, the monitoring board recommended closing the study because it concluded that the results were definitive for both acupuncture and amitriptyline comparisons.

RESULTS

Study Population

From May 1993 to February 1997, 250 patients were enrolled. Of those, 239 were in the acupuncture comparison (125 in the factorial option and 114 randomized to SAR or control points), and 136 were in the amitriptyline comparison (125 from the factorial option and 11 randomized to either active or placebo amitriptyline) (Figure 2). Baseline characteristics (Table 1) were similar in the active and control groups for both comparisons.

Table 2.—Mean Changes in Weekly Pain Diary Scores, Neurologic Score, and Quality of Life at 6 and 14 Weeks*

	Acupuncture						Amitriptyline Hydrochloride					
	SAR		Control Points				Active		Placebo			
	No.	Mean Change	No.	Mean Change	Difference (95% CI)†	*P* Value†	No.	Mean Change	No.	Mean Change	Difference (95% CI)‡	*P* Value‡
Primary Outcomes												
Pain diary, 6 wk	112	−0.21	93	−0.20	0.01 (−0.11 to 0.12)	.88	56	−0.23	54	−0.18	−0.07 (−0.22 to 0.08)	.38
Pain diary, 14 wk	105	−0.29	82	−0.19	−0.08 (−0.21 to 0.06)	.26	49	−0.26	52	−0.30	0.00 (−0.18 to 0.19)	.99
Secondary Outcomes												
Neurologic score, 14 wk	94	2.1	80	−1.4	2.2 (−1.9 to 6.3)	.30	49	0.8	49	−0.4	0.6 (−4.3 to 5.4)	.82
Quality of life												
Physical functioning, 6 wk	110	6.0	102	5.6	0.4 (−5.4 to 6.1)	.90	61	5.9	60	5.1	0.3 (−8.3 to 8.9)	.94
Physical functioning, 14 wk	97	3.4	90	1.3	3.4 (−3.3 to 10.0)	.32	52	7.1	51	0.6	6.4 (−2.7 to 15.5)	.17
Overall *P* value, 14 wk§						.64						.60

*SAR indicates standardized acupuncture regimen; CI, confidence interval.
†SAR minus control points, adjusted for unit, baseline score, and amitriptyline assignment (active, placebo, or none).
‡Active minus placebo, adjusted for unit, baseline score, and acupuncture assignment (SAR or not SAR).
§*P* value from combining 11 dimensions using method of O'Brien.[23]

Effects of Treatment

SAR vs Control Points.—The change in pain was not significantly different between the 2 groups at either 6 or 14 weeks (Table 2). Both groups showed improvement in pain from an average intensity of "moderate" to "mild" (Figure 3). The estimated difference of the SAR group compared with the control points group was 0.01 at 6 weeks (95% confidence interval [CI], –0.11 to 0.12; $P = .88$) and –0.08 at 14 weeks (95% CI, –0.21 to 0.06; $P = .26$). At 6 weeks, the SAR group had less pain relief than patients in the control points group by 0.01 U and at 14 weeks, the SAR group had 0.08 U more relief than patients in the control points group. Repeated measures analyses of weekly pain averages during the entire 14-week period gave weekly effects, which were small and nonsignificant (*P* values ranging from .10 to .94).

There were no significant differences in the quality of life, neurologic summary score (Table 2), number of grade 4 adverse events, deaths, or discontinuations. By 14 weeks, 20% of patients randomized to the SAR group and 25% of those randomized to control points group had discontinued treatment. Three patients assigned to the SAR option and 10 assigned to the control points experienced a grade 4 adverse event ($P = .06$).

The difference in the global pain relief rating between the 2 groups was not significant at 6 weeks ($P = .65$). However, at 14 weeks, there was a nominally significant difference ($P = .03$) with a slightly higher proportion of patients in the SAR group reporting moderate or more pain relief than those in the control points group (Table 3). However, after adjustment for multiple comparisons, the result is not significant.

Amitriptyline vs Placebo.—The change in pain score at 6 and 14 weeks was not significantly different between the active and placebo groups (Table 2). As with the SAR vs control points comparison, both groups showed improvement over time (Figure 3). The estimated difference of amitriptyline compared with placebo was –0.07 at 6 weeks (95% CI, –0.22 to 0.08; $P = .38$) and 0.00 at 14 weeks (95% CI, –0.18 to 0.19; $P = .99$). That is, at 6 weeks, patients taking amitriptyline had more pain relief by 0.07 U than those taking placebo and there was no difference at 14 weeks. Repeated measures analyses of weekly pain averages indicated that the largest beneficial effect was at week 3 ($P = .05$), but after adjusting for multiple comparisons, the result was not statistically significant.

There were no statistically significant differences in quality of life, neurologic summary scores (Table 2), number of grade 4 adverse events, or deaths. Six patients assigned to the amitriptyline and 2 assigned to placebo options experienced grade 4 adverse events ($P = .20$). By 14 weeks, 35% of patients randomized to either the amitriptyline or placebo groups had discontinued drug treatment. The difference in the global pain relief rating between the 2 groups was not significant at 6 weeks ($P = .68$) or 14 weeks ($P = .81$) (Table 3).

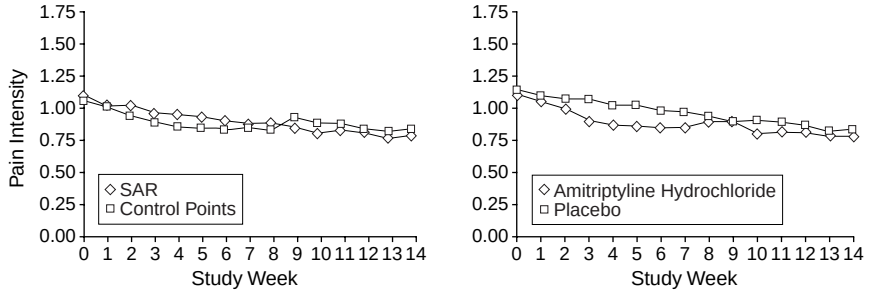

Figure 3.—Average pain intensity scores for single factor options by study week. The mean weekly values of the descriptors of pain intensity are plotted. There was no statistically significant difference between the effects of the standardized acupuncture regimen (SAR) vs control points or between amitriptyline vs placebo. Pain intensity is described and rated as no pain (0.0), faint (0.04), very weak (0.36), weak (0.45), very mild (0.59), mild (0.74), moderate (1.09), barely strong (1.10), slightly intense (1.35), strong (1.36), intense (1.59), very intense (1.64), and extremely intense (1.75).[18]

Factorial Option.—The test for interaction in change of pain between the 2 factors was not significant at either 6 or 14 weeks ($P = .17$ and $P = .31$, respectively). There was no significant difference in the change in pain among the 4 groups at either 6 or 14 weeks ($P = .37$ and $P = .64$, respectively). All study groups in the factorial option showed improvement in pain.

Completeness of Data

Figure 2 shows the number of patients providing pain diary data and global pain relief ratings at 6 and 14 weeks. To examine the sensitivity of the conclusions to missing data, the analyses were repeated using 2 common methods to impute missing data. The first assumes that the patients' missing data indicated no change in their pain from baseline; the second uses the last value of the weekly pain reported to calculate the end point. Under both methods to impute the missing pain diary data, the results of the study did not reach statistical significance for either comparison at either 6 or 14 weeks.

Table 3.—Global Pain Relief Rating at 6 and 14 Weeks*

	Acupuncture				Amitriptyline Hydrochloride			
	SAR		Control Points		Active		Placebo	
Global Pain Relief	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %
6 weeks								
Complete	3	2.7	2	1.9	3	4.9	3	5.0
A lot	17	18.0	14	15.5	6	14.8	10	21.7
Moderate	37	51.4	36	50.5	22	50.8	15	46.7
Slight	29	77.5	19	68.9	14	73.8	13	68.3
None	16	91.9	22	90.3	11	91.8	11	86.7
Pain worse	9	100.0	10	100.0	5	100.0	8	100.0
No. of patients with rating	**111**		**103**		**61**		**60**	
P value†			.65				.68	
14 weeks								
Complete	8	7.8	2	2.1	1	1.7	0	0.0
A lot	19	26.5	27	30.9	12	22.4	12	22.6
Moderate	31	56.9	16	47.9	14	46.4	15	50.9
Slight	23	79.4	18	67.0	13	69.0	13	75.5
None	19	98.0	26	94.7	16	96.6	11	96.2
Pain worse	2	100.0	5	100.0	2	100.0	2	100.0
No. of patients with rating	**102**		**94**		**58**		**53**	
P value†			.03				.81	

*SAR indicates standardized acupuncture regimen.
†Likelihood ratio test for the conditional independence of relief and treatment arm; SAR vs control points comparison is adjusted for the level of the other factor (active amitriptyline, placebo amitriptyline, and no amitriptyline). Amitriptyline vs placebo comparison is adjusted for the level of the other factor (SAR, control points, or no acupuncture).

Table 4.—Effectiveness of Participants' Blinding to Treatment Assignment*

	Acupuncture, No. (%)			Amitriptyline Hydrochloride, No. (%)	
Patient Guess	SAR	Control	Patient Guess	Active	Placebo
Moderate or more relief†					
SAR	47 (81.0)	28 (62.2)	Active	20 (74.1)	9 (33.3)
Control points	2 (3.4)	6 (13.3)	Placebo	4 (14.8)	16 (59.3)
Cannot guess	9 (15.5)	11 (24.4)	Cannot guess	3 (11.1)	2 (7.4)
Less than moderate relief†					
SAR	14 (31.8)	10 (20.4)	Active	19 (61.3)	8 (30.8)
Control points	12 (27.3)	22 (44.9)	Placebo	6 (19.4)	15 (57.7)
Cannot guess	18 (40.9)	17 (34.7)	Cannot guess	6 (19.4)	3 (11.5)
P value‡		.02			<.001

*SAR indicates standardized acupuncture regimen.
†Global pain relief rating at 14 weeks.
‡Likelihood ratio test for independence of guess and treatment adjusted for global pain relief rating at 14 weeks (moderate or more vs less than moderate).

Assessment of Treatment Blinding

For the acupuncture comparison, although the patients' guesses and the treatment assignments were not independent ($P = .007$, data not shown), there was a strong association between the guess and the global pain relief rating. Those reporting moderate or more relief at 14 weeks tended to guess that they received the SAR. After adjusting for option and the reported relief being moderate or more, the patients' guesses and the treatment assignments were not independent ($P = .02$), but the association was small. This differed in the amitriptyline comparison, in which a large proportion of patients correctly guessed the study treatment, irrespective of their level of pain relief ($P < .001$) (Table 4).

COMMENT

The main findings of this study show that treatment with this SAR had little or no effect on HIV-related peripheral neuropathy compared with the control points. Similarly, amitriptyline, as commonly used, was not significantly more effective than placebo (Table 2 and Figure 3). All treatment groups improved during the study period by the amount hypothesized in the design, suggesting that the modest decline in pain scores in all groups was either attributable to a placebo effect or patients entered the study at times of symptomatic flares and improved spontaneously thereafter.

For the acupuncture comparison, the results were strengthened by 2 methodological features of the trial. First, the sample size of approximately 120 patients per treatment group is many times larger than those in previously published trials of acupuncture,[9] and the CIs were narrow, making it unlikely that a large positive treatment effect was missed by chance. Second, the control points appeared reasonably effective in preserving the blinding (Table 4). Many of the study clinicians and, presumably, the study participants were favorably disposed toward acupuncture. If patients were able to guess their treatment better than randomly, the resulting placebo effects would be expected to bias the result in favor of this SAR,[10,12,24] thus making our finding of a similar effect even more convincing.

We cannot completely rule out the possibility that the SAR had a modest and delayed analgesic effect, in view of the nominally significant result of SAR compared with control points on the global pain relief rating at 14 weeks, although this was not seen at 6 weeks. This is unlikely, however, in view of the finding of no significant difference in the pain diary scores. Our study was designed with a sample size that provided sufficient power to detect even a small difference between the SAR and control points. The CIs at both 6 and 14 weeks rule out any clinically meaningful beneficial effects of SAR based on the primary end point of the pain diary scores.

One possible explanation for the lack of efficacy of the SAR is that we chose the wrong "active points." Consensus on the SAR was reached by 8 acupuncturists before protocol implementation. Another explanation is that the use of nonclassical points as a control provided a real effect and was not an inert control. There is evidence from animal and human studies that acupuncture at either classical or nonclassical locations may have analgesic effects[9,25,26] by mechanisms such as the release of endogenous opioids[27] or activation of other brain and spinal cord pathways that reduce pain.[28]

There is controversy over what constitutes an acceptable control group for acupuncture studies.[8,29] It is possible that the novelty of an experience like acupuncture may generate a placebo analgesic effect quite apart from specific effects produced by needling specific points.[30] Unless the study includes a "sham" acupuncture group as a control, such nonspecific effects may bias toward a result in favor of the active intervention.

The SAR chosen for this study differs from the practice of most acupuncturists, who treat patients with individualized regimens.[31] We chose to study standardized points to test the hypothesis that these specific points promote analgesia for chronic foot and leg pain[13] and because such a study is easier to blind and replicate. If the acupuncturists had used indi-

vidualized treatment, the results would not be generalizable to other acupuncturists, and the treatment, if efficacious, could not be used by other practitioners. Our approach enabled us to derive a conclusion about these acupuncture points but not about individualized treatments.

Amitriptyline is used in the treatment of HIV-related peripheral neuropathy[32] but was not effective in this study. The lack of efficacy at 14 weeks was confirmed by the analysis of the secondary end points. Although the 6-week CI did not completely rule out the beneficial effect of 0.20 that the study was designed to detect, there was no supporting evidence of beneficial effect from any of the secondary end points. In addition, another study in HIV-related peripheral neuropathy agrees with our findings.[33] The indication that the blinding was not maintained also confirms the lack of efficacy because unblinding tends to bias toward a hypothesized active intervention.[24,34]

It is possible that a higher dose of amitriptyline would have resulted in a larger treatment effect. We chose this dose based on common clinical practice and on the only 2 published prospective randomized dose-response studies of tricyclic antidepressants used for chronic pain.[15,16]

No previously controlled trials of amitriptyline in neuropathic pain have followed up patients for longer than 8 weeks.[33,35] Clinical trials of amitriptyline for neuropathies of diabetic and nondiabetic etiologies have shown larger, short-term, clinically meaningful effects.[6,7,19] Mechanisms for this include facilitation of the analgesic action of norepinephrine and serotonin released by endogenous analgesic systems[16,19] and the blockade of sodium channels in peripheral sprouts from damaged nerves.[36] Presumably, the neuropathological features of the HIV-associated distal axonal neuropathy generate painful discharges resistant to the analgesic actions of tricyclic antidepressants.[37,38]

In conclusion, this is the largest reported randomized, placebo-controlled, clinical trial of symptomatic treatment for HIV-related peripheral neuropathy. Overall, our results indicate that neither this SAR given over 14 weeks nor amitriptyline hydrochloride, 75 mg/d, was effective in relieving pain and neither therapy can be recommended for the treatment of HIV-related peripheral neuropathy. Additional clinical trials are needed because there are no effective treatments for this chronic debilitating condition.[39]

This project was supported by the National Institute of Allergy and Infectious Diseases.

We are indebted to the study participants for their cooperation and support and to other members of the Community Programs for Clinical Research on AIDS, who are as follows: Carol Anne Bosco, RN, Jill Chesnut, RN, MED, Jeffrey Cohen, MD, Marjorie Dehlinger, DNSc, Sister Mary Sarah Dolan, RN, Valerie Dratter, RN, MS, Lawrence Fox, MD, PhD, Ana Martinez, RpH, Jim Neaton, PhD, Marie Sioud, and Wendy Smith, PhD; and to Peter Jatlow, MD, for determining amitriptyline blood levels. We thank Zarina Alloo, Coleen Craig, Susan Meger, and Michelle Puplava for preparation of the manuscript. We also thank the members of the National Institute of Allergy and Infectious Diseases HIV Therapeutic Trials Data Safety and Monitoring Board, who are as follows: Baruch A. Brody, MD, Charles Carpenter, MD, David DeMets, PhD, Thomas R. Fleming, PhD, Mary A. Foulkes, MPH, PhD, Bernard Lo, MD, Julio Montaner, MD, Dianne Murphy, MD, Judith O'Fallon, PhD, James Rahal, MD, Wasima Rida, PhD, Steven Schnittman, MD, Paula Sparti, MD, Patricia N. Whitley-Williams, MD, Robert Woolson, PhD, and Abigail Zuger, MD. The following institutions and persons participated in the Community Programs for Clinical Research on AIDS: Philadelphia Fight, Philadelphia, Pa (Barbara Gallagher, Gary Seely, Regina Anthony); Denver Community Program for Clinical Research on AIDS, Denver, Colo (Michael Grodesky, Brenda Hughston, Jack Rouff); Harlem AIDS Treatment Group, New York, NY (Wafaa El-Sadr, Mary Sarah Dolan, Luis Fuentes); Community Consortium, San Francisco, Calif (Sherill Crawford, Margaret Poscher, John Nienow); Clinical Directors Network of Region II, Inc, New York, NY (Anita Vaughn, Jo Anne Staats, Margaret Granville); The Research and Education Group, Portland, Ore, (James Sampson, Doug Beers, Joyce St Arnaud); Partners in Research/New Mexico, Albuquerque (Bruce Williams, Nadine Ulibarri-Keller, Cynthia Geist); Baltimore Trials, Baltimore, Md (David Wheeler, Louise Pascal, Sandra Jones); Wayne State University, Detroit, Mich (Randa Fakhry, Rodger MacArthur, Michael Shy); North Jersey Community Research Initiative, Newark, NJ (Catherine Forrester, Norma Santos); and Washington Regional AIDS Program, Washington, DC (Douglas Ward, Barbara Standridge). In addition, the following acupuncturists participated in the study: Beverly Bakken, DOM, Dipl NCCA, Marijke S. de Vries, DOM, Andrew Fitzcharles, L Ac, Lee Forest Knowlton, L Ac, Dipl Ac, Skya Gardner-Abbate, MA, DOM, Dipl Ac, Magnolia Goh, MD, L Ac, Christopher Hudson, L Ac, Joel Kay, MD, Robert Kelly, OMD, Dipl Ac, Lixing Lao, PhD; Lorna Lee, RAc, Patricia R. Lollis, L Ac, Howard Moffet, MPH, L Ac, Joseph Odom, L Ac, Lahary Pittman, CA, CAC, Eric Serejski, M Ac, L Ac, Dipl Ac, Qing-Yao Shi, MD, L Ac, Deborah Torrance, Dipl Ac, CA, Lynsay Tunnell, DOM, Byrn Walsh, L Ac, and Wendy Whitman, L Ac.

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